

ROLE OF ORAL ANTICOAGULATION IN MANAGEMENT OF ATRIAL FIBRILLATION

813

Eugene Crystal, Stuart J Connolly

Heart 2004;90:813–817. doi: 10.1136/hrt.2003.021642

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia, with an estimated prevalence of two million in the USA.¹ AF carries significantly increased risk of morbidity and mortality, a major component of which is a fivefold increase in the frequency of stroke.² Non-rheumatic AF is probably responsible for 15–20% of cerebrovascular accidents of ischaemic origin.^{3 w1} The risk of embolic stroke in the general population increases with age; in people over the age of 75 years AF is one of the most important causes of embolic stroke.⁴

A majority of the cerebrovascular events in AF patients are ischaemic.⁵ A principal mechanism responsible for ischaemic stroke in AF is embolism secondary to the stasis in the left atrium, specifically in the left atrial appendage. Thrombogenesis in AF patients is correlated with low flow velocities in the appendage.^{w2} The left atrial appendage is the almost exclusive location of intracardiac thrombus in patients with AF.^{w3} Overall in AF, two thirds of the ischaemic cerebrovascular events and perhaps half of all vascular events are related to the atrial thrombi.⁴

The other implicated cause of stroke in AF patients is coexisting atherosclerosis of the large arteries and valvar abnormalities. Indeed, many of the patients with AF are at increased risk of significant carotid disease.^{w4} Notably, the major risk factors for stroke in patients with AF are the same as the risk factors for accelerated atherosclerosis (table 1). Clinically active atherosclerotic disease is very common in patients with AF. In the SPAF (stroke prevention in atrial fibrillation) trial (mean age of patients 67 years) 10% of patients had active angina, 8% had had a myocardial infarction, and 12% had significantly decreased left ventricular function.⁶ The overall mortality in placebo treated patients with AF was 3.1% annually, with seven out of eight fatal events being of cardiovascular origin. Some experimental data suggest that AF related haemodynamics may actually increase the propensity for arterial thrombosis in narrowed vessels.^{w5}

The risk of stroke varies significantly between patients with AF. The main risk factors identified in two major studies addressing the issue in AF patients are presented in table 1. The history of prior embolic event and age are the two most powerful predictors of increased risk of stroke in non-valvar AF.

PREVENTION OF STROKE IN AF PATIENTS

The goal of decreasing the risk of stroke in AF has been approached with two treatment concepts: antiarrhythmic therapy (aimed at suppression of AF, also known as rhythm control), and antithrombotic treatment (aimed at suppression of coagulation cascade and platelet activation).^{w6} Mechanical approaches, based on the obstruction of the left atrial appendage, are now also under evaluation.^{w3 w7 w8}

Four very recent randomised trials examined whether rhythm control is able to decrease the risk of death or embolic stroke in AF^{6–9} when compared to rate control alone. All of these trials consistently reported failure to decrease the risk of embolic events in AF patients. Therefore, the only currently credible option for preventing vascular events in AF patients is antithrombotic treatment, which is the focus of this review.

ORAL ANTICOAGULANTS

The coumarin anticoagulants include warfarin, dicumarol, and several related compounds. Their main mechanism of action is prevention of the intrahepatic metabolism of vitamin K epoxides, and an induction of vitamin K deficiency. As a result, thrombin generation slows, and clot formation becomes impaired due to decreased biologic activity of the prothrombin complex proteins. The effect of vitamin K antagonists is gradual and reversible. It takes several days before an adequate level of anticoagulation is achieved, and for the anticoagulant effect to disappear after drug discontinuation.

The therapeutic effect of oral anticoagulants (OACs) is measured by monitoring the prothrombin time. OAC dosage must be adjusted to achieve a narrow range of the desired prothrombin time values, usually expressed as the international normalised ratio (INR). Thromboplastins, the essential reagent for prothrombin time testing, vary in animal source and

See end of article for authors' affiliations

Correspondence to:
Eugene Crystal, MD, Division
of Cardiology, Sunnybrook
and Women's College Health
Science Centre, 2075 Bayview
Avenue, Toronto, Ontario
M4N 3M5, Canada; eugene.
crystal@sw.ca

Table 1 Risk factors of embolism in AF patients (only independently significant factors included)

Risk factor	Associated relative risk by AFI investigators ^{w23}	Associated relative risk by SPAF investigators ¹⁹
Prior stroke or transient ischaemic event	2.5	2.9
Diabetes mellitus	1.7	–
Age	1.6/decade	1.8/decade
Hypertension	1.6	2.0
Alcohol consumption	–	0.4
Female sex	1.6	–

SPAF, stroke prevention in atrial fibrillation.

method of preparation, which result in differing sensitivities to factor deficiencies. Differences in instrumentation, methodology, and control plasmas also contribute to inter- and intra-laboratory variability. To control for this the World Health Organization has established a reference thromboplastin derived from human brain that is now used to calibrate secondary standards, and is available to manufacturers and laboratories for the evaluation of thromboplastin reagents. In an effort to standardise the monitoring of OAC, the INR was adopted worldwide. The INR converts the prothrombin (PT) patient/PT mean normal ratio to the value expected if the test had been performed with the WHO reference thromboplastin.

The OAC antagonists have multiple interactions with other drugs and some food components. The most common agents associated with enhanced anticoagulant effect are allopurinol, common analgesics, antiarrhythmics, antidepressants, antidiabetics, antimalarials, antiplatelets, anxiolytics, disulfiram, levothyroxine, lipid regulating agents, testosterone, and alcohol. Oral contraceptives, raloxifene, retinoids, rowachol, and vitamin K have the opposite, reducing effect on anticoagulation.

The most common contraindications for OACs include evidence of any active bleeding, uncontrolled severe hypertension, recent brain, eye or spinal cord surgery or injury, propensity for recurrent falling, inability for INR monitoring, and patient non-compliance.^{w9}

ORAL ANTICOAGULANTS IN AF

By the late 1990s, six randomised clinical trials addressing the efficacy of OACs in non-valvar AF by comparison to placebo or no treatment had been published^{15–14} (table 2). The data from these and other trials of OACs were recently summarised in a meta-analysis.¹⁵ In all these trials OAC treatment was associated with decreased risk of ischaemic

Three concepts of stroke prevention in AF

1. Antithrombotic treatment—anticoagulant or antiaggregant effects aimed at diminishing the pro-thrombotic effects of atrial fibrillation
2. Antiarrhythmic treatment—aimed at eliminating atrial fibrillation or significantly decreasing the burden of atrial fibrillation
3. Mechanical means—aimed at the occlusion of the left atrial appendage, or protecting the internal carotid artery from thrombi

stroke in patients with AF, with a relative risk reduction in the range of 33–75%, mean 62% (95% confidence interval (CI) 48% to 72%). The effect of OAC was consistent and was achieved despite overall 20% dropout rates.

The absolute benefit of OAC in patients with AF varies in the placebo controlled studies according to the risk of embolic events in the patient population enrolled: the higher the risk of cardioembolic event, the stronger the absolute preventive benefit from anticoagulation (fig 1). The overall effect of OAC was a 59% reduction in stroke in the primary prevention trials and 68% in the secondary prevention trial. The absolute annual risk reduction for all strokes was 2.7% for the primary prevention and 8.4% for the secondary prevention trials (number needed to treat for one year to prevent one stroke was 37 and 12, respectively). Total mortality also decreased with OAC significantly, with relative risk reduction of 26% (95% CI 4% to 43%) and an absolute risk reduction of 1.6% per year.¹⁵

The range of efficacy of the oral anticoagulants evaluated in the randomised trials differed significantly (with a lower INR range of 1.5–2.8, and an upper range of 2.7–4.5). When estimated in a case-control study, the lower threshold of intensity of anticoagulation in patients with a history of embolic stroke was an INR of 2.0.^{w10} The probability of stroke increases steeply in patients having an INR < 2.0. The upper limit of safe INR is between 3.0–4.0, varying significantly with the risk of intracranial haemorrhage. The INR ratios recommended by the most recent guidelines are 2.0–3.0, with a target level of 2.5.^{16 w6}

WARFARIN IN AF COMPARED TO OTHER REGIMENS

Antiplatelet regimens are another prophylactic modality available for treating patients with AF which have been evaluated in randomised clinical trials and subsequent meta-analyses.^{w11 w12} In primary prevention trials aspirin reduces stroke and major vascular events in non-valvar AF by 22%.^{w11} A single secondary prevention trial demonstrated a

Table 2 Adjusted dose warfarin compared with placebo, or no treatment in non-rheumatic AF (modified from Hart and colleagues¹⁵)

Study	Prevention	Target INR	Warfarin group: strokes/ person-years	Placebo group: strokes/ person-years	Relative risk reduction (%)	Absolute risk reduction per year (%)
Petersen ¹⁰	Primary	2.8–4.2	9/413	19/336	54	2.6
SPAF ⁵	Primary	2.0–4.5	8/263	19/245	60	4.7
BAATAF ¹¹	Primary	1.5–2.7	3/487	13/435	78	2.4
Connolly ¹²	Primary	2.0–3.0	6/237	9/241	33	1.2
Ezekowitz ¹³	Primary	1.4–2.8	7/489	23/483	70	3.3
EAF ¹⁴	Secondary	2.5–4.0	20/507	50/405	68	8.4
All trials			53/2396	133/2207	62 (48 to 72)*	3.1

BAATAF, Boston area anticoagulation trial for atrial fibrillation; EAF, European atrial fibrillation trial; INR, international normalised ration; SPAF, stroke prevention in atrial fibrillation.

*95% confidence interval.

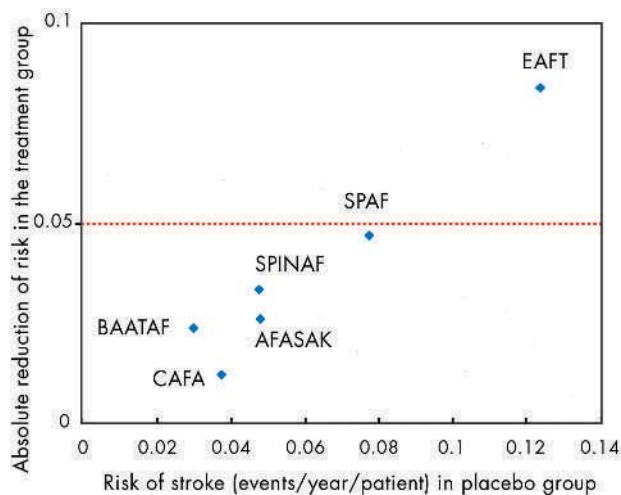


Figure 1 Absolute benefit in stroke prevention by anticoagulation versus placebo. AFASAK, Copenhagen atrial fibrillation, aspirin and anticoagulant therapy study; BAATAF, Boston area anticoagulation trial for atrial fibrillation; CAFA, Canadian atrial fibrillation anticoagulation trial; EAFT, European atrial fibrillation trial; SPAF, stroke prevention in atrial fibrillation trial; SPINAF, Veterans Affairs stroke prevention in non-rheumatic atrial fibrillation trial.

non-significant reduction in the risk of recurrent stroke from 12% to 10% per year (odds ratio (OR) 0.89, 95% CI 0.64 to 1.24).^{w12}

More than 10 randomised comparative trials compared dose adjusted OACs with other drug regimens for the stroke prevention in AF. Three recent meta-analyses have reviewed these data.^{15 17 w13} The results of these meta-analyses are consistent in regard to the superiority of OAC over antiplatelet treatment, but differed in regard to the extent of this superiority. This difference may be explained by the inclusion of trials comparing OAC to the combination of low dose warfarin and aspirin¹⁷ and inclusion of antiplatelet regimens other than aspirin.^{w13}

The only individual patient data based meta-analysis¹⁷ was limited to the comparisons of warfarin and aspirin (excluding

trials on other antiplatelets drugs and including two trials which used a combination of aspirin and low dose warfarin). This meta-analysis reported a significant superiority of the OAC over aspirin in the prevention of all strokes (hazard ratio (HR) 0.55, 95% CI 0.43 to 0.71) and cardiovascular events (HR 0.71, 95% CI 0.59 to 0.85) (fig 2). It did not find a significant reduction of mortality (HR 0.93, 95% CI 0.76 to 1.13). OAC (compared to aspirin) prevented 2.1 strokes (decrease of stroke rate from 4.5/100 patient-years to 2.4/100 patient-years) at a cost of approximately 1.1 major bleeds (increase in the major bleeding rate from 1.3/100 patient-years in aspirin group to 2.2/100 patient-years (relative risk (RR) 1.17, 95% CI 1.21 to 1.41)).

Interestingly, another recent meta-analysis compared OAC with any evaluated antiplatelet agents (excluding trials where the combination of aspirin and warfarin was compared to warfarin) and showed no significant difference between OAC and antiplatelet treatment with regard to vascular death or fatal strokes, with only statistically borderline superiority of OAC for outcome of non-fatal stroke (OR 0.68, 95% CI 0.46 to 0.99).^{w13} The incidence of the major bleeding event was higher with OACs (OR 1.45, 95% CI 0.93 to 2.27). Major bleeding in the aspirin arm in this meta-analysis may be inflated due to inclusion of low dose warfarin in this arm.

Thus, the accumulated evidence certainly indicates the superiority of oral anticoagulation over aspirin treatment alone in patients with AF at increased risk of stroke. However, the magnitude of the benefit of OAC over antiplatelet agents remains slightly uncertain. Data suggest that the effect on stroke is more powerful than against other vascular events. OAC is currently the gold standard for prevention of stroke and other vascular events in AF patients.

LIMITATIONS OF ORAL ANTICOAGULATION

The limitations of OAC are significant and the main concerns are safety and adherence to the treatment.

Chronic OAC use is associated with a significant increase in the risk of major bleeding, including haemorrhagic stroke. The absolute of this increase depends on the level of

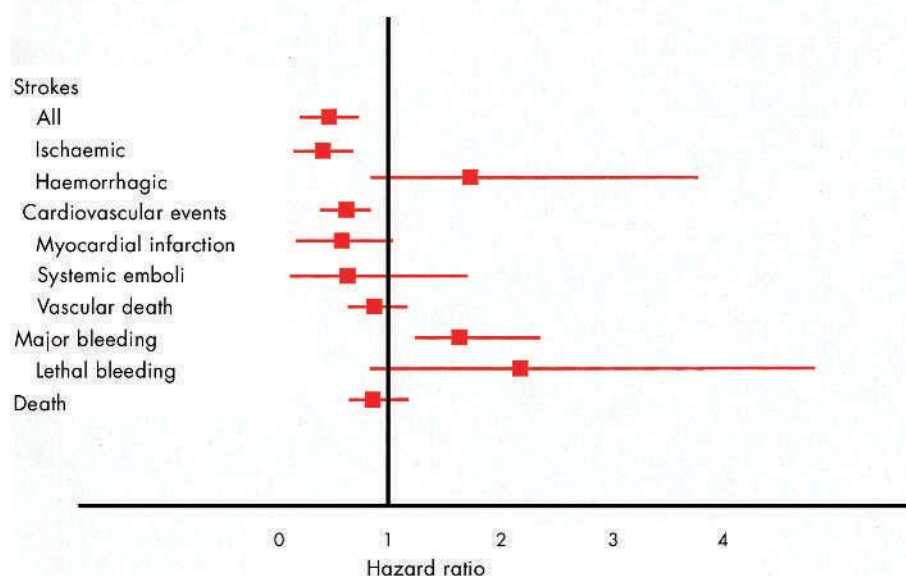


Figure 2 Comparison of oral anticoagulants and aspirin.¹⁷

OAC versus placebo

- ▶ Significant stroke reduction in primary and secondary prevention
- ▶ Significant reduction in total mortality.

816

anticoagulation, but in participants of randomised controlled trials receiving active drug it is generally estimated as 0.2% per year for haemorrhagic stroke (from 0.1% in the placebo group to 0.3% in the OAC group), and 0.3% for major extracranial haemorrhage (from 0.6% to 0.9%). The overall rate of haemorrhagic events has been reported to be as high as 1.8% per year in AF patients over 75 years of age.¹⁸ The risk of major haemorrhage during OAC when compared to aspirin was 2.2 versus 1.3 per 100 patient-years (HR 1.71, 95% CI 1.21 to 2.41) (note that the annual risk with aspirin was actually lower than that of placebo).¹⁷ The increase in risk of brain haemorrhage in the same meta-analysis was not significant (0.5 v 0.3 per 100 patient-years (HR 1.84, 95% CI 0.87 to 3.87)).

The risk of the brain haemorrhage is higher in routine practice than in rigorously controlled clinical trials.^{w14 w15} Recognised independent risk factors for major bleeding events are elevated INR, history of stroke, history of gastrointestinal bleeding, and serious co-morbid conditions.^{w15 w16}

Poor patient adherence to the treatment, drug interactions, and multiple dietary restrictions make it difficult to remain in the recommended range of INR. Chronic anticoagulant therapy places the patient under a number of restrictions, including delays of urgent invasive procedures, contraindication for thrombolytic treatment for myocardial infarction, and potentially serious bleeding after common trauma. Many patients need to discontinue anticoagulants for other treatments and procedures during which time they are at risk.

In spite of the evidence and recommendations, only about half of all patients with AF are correctly treated.^{w17-19} Old and disabled AF patients are even less likely to receive OAC.^{w17-19} Even in patients who have no contraindications to OAC, there are several patient, physician, and health care system related barriers to the prescription of OACs.^{w18} Patients with AF before the first stroke are less likely to receive adequate OAC than after having one.^{w18}

Specifically oriented clinics of anticoagulation have been reported to make OAC more effective, safe, and even cost effective.^{w20} The greater use of self monitoring devices could further improve safety and efficacy of this treatment.^{w21}

RECOMMENDATIONS

Two major guidelines addressing the use of OAC in patients with AF are available.^{16 w22} Both indicate that AF in combination with one or more risk factors for a thromboembolic event is a class I indication for OAC administration. Risk factors include history of prior cerebrovascular or other systemic embolic event, hypertension, age > 75 years, poor left ventricular function, rheumatic heart disease, or a prosthetic valve. Both guidelines are targeting the same levels of anticoagulation in these patients (INR 2.0–3.0).

Management of those patients at moderate risk (with one of the indicators of moderate risk: diabetes, age 65–75 years, thyrotoxicosis, coronary artery disease) is clearly addressed in the American College of Chest Physicians consensus, where use of either OAC or aspirin is recommended.

OAC versus antiplatelet treatment

- ▶ Significant reduction of all strokes
- ▶ Significant reduction of cardiovascular events

CONCLUSION

Currently, chronic OAC treatment is the most effective available prophylactic approach in patients with AF at high risk of thromboembolic events. Aspirin, the only available proven alternative to chronic OAC, is significantly less effective, and therefore is only indicated in patients at moderate and low risk, or in patients with major contraindications to OAC. Chronic OAC, however, is underused, due to contraindications and difficulties in its use.

Therapeutic agents as effective as OACs, with greater ease of use and fewer contraindications, are being tested and may offer improved antithrombotic protection for patients with AF in the future.

Authors' affiliations

E Crystal, Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

S J Connolly, Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

REFERENCES

- 1 **American Heart Organization**. 2001 Heart and stroke statistical update. Dallas, Texas: American Heart Association, 2001:18.
- 2 **Wolf PA**, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;**22**:983–8.
- 3 **Flegel KM**, Shipley MJ, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. *Lancet* 1987;*i*:526–9.
- 4 **Hart RG**, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. *Stroke* 2001;**32**:803–8.
- ▶ **Comprehensive editorial review of the concepts behind the use of oral anticoagulants, with in-depth discussions of associated controversies.**
- 5 **SPAF Investigators**. Stroke prevention in atrial fibrillation study. Final results. *Circulation* 1991;**84**:527–39.
- 6 **Hohnloser SH**, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation—pharmacological intervention in atrial fibrillation (PIAF): a randomised trial. *Lancet* 2000;**356**:1789–94.
- 7 **Van Gelder IC**, Hagens VE, Bosker HA, *et al*. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–40.
- 8 **Wyse DG**, Waldo AL, DiMarco JP, *et al*. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–33.
- ▶ **Largest of existing trials on the rhythm versus rate control. The study showed no survival benefit of rhythm control strategy by pharmacological means over rate control approach.**
- 9 **Carlsson J**. STAF – a randomized trial of strategies in atrial fibrillation. *J Am Coll Card* 2001;**38**:603A.
- 10 **Petersen P**, Boysen G, Godtfredsen J, *et al*. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet* 1989;*i*:175–9.
- 11 **BAATAF Investigators**. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston area anticoagulation trial for atrial fibrillation investigators. *N Engl J Med* 1990;**323**:1505–11.
- 12 **Connolly SJ**, Laupacis A, Gent M, *et al*. Canadian atrial fibrillation anticoagulation (CAFA) study. *J Am Coll Cardiol* 1991;**18**:349–55.
- 13 **Ezekowitz MD**, Bridgers SL, James KE, *et al*. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs stroke prevention in nonrheumatic atrial fibrillation investigators. *N Engl J Med* 1992;**327**:1406–12.
- 14 **European Atrial Fibrillation Trial Study Group**. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European atrial fibrillation trial) study group. *Lancet* 1993;**342**:1255–62.
- 15 **Hart RG**, Benavente O, McBride R, *et al*. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**:492–501.
- 16 **Fuster V**, Ryden LE, Asinger RW, *et al*. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines and policy conferences (committee to develop guidelines

for the management of patients with atrial fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *Circulation* 2001;**104**:2118–50.

- ▶ **The most recent comprehensive guidelines on the management of the atrial fibrillation, including use of oral anticoagulants.**
- 17 **van Walraven C**, Hart RG, Singer DE, *et al*. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;**288**:2441–8.
- ▶ **Individual patient data meta-analysis comparing oral anticoagulation and antiplatelet regimens demonstrated significant superiority of oral anticoagulation in end points of stroke and all cardiovascular events.**
- 18 **Wolf PA**, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med* 1987;**147**:1561–4.

- 19 **Hart RG**, Pearce LA, McBride R, *et al*. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I–III clinical trials. The stroke prevention in atrial fibrillation (SPAF) investigators. *Stroke* 1999;**30**:1223–9.



Additional references appear on the *Heart* website—<http://www.heartjnl.com/supplemental>

817

LEARNING ON THE WEB

Case 6: Aortic valve replacement in the elderly

Roger Hall, Professor of Clinical Cardiology, University of East Anglia, Norwich, Norfolk, UK

Mark Earley, St Bartholomew's Hospital, London, UK

A 90 year old man was found at home by his daughter, slumped at the bottom of his stairs. He recalled quite severe tight central chest pain associated with breathlessness and sweating while going up stairs which was not relieved by taking a spray of sublingual glyceryl trinitrate (GTN). He sensed that he was “about to die” before collapsing with loss of consciousness. He was sent to the accident and emergency department (emergency room) of his local hospital by ambulance.

The patient had a five year history of angina pectoris that limited him to one flight of stairs within the house and light housework only. Over the two weeks preceding his admission to hospital he had experienced increasing frequency of these symptoms and used his GTN spray more often than usual. He had not smoked for over 50 years and there were no other risk factors for cardiovascular disease. There was no other notable past medical history and he was otherwise fit, living completely independently.

The significance of these signs and symptoms, the diagnosis, and the short and long term treatment of these problems are discussed in an interactive case presentation.